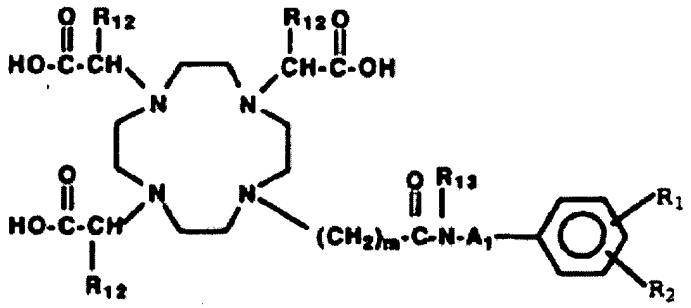
Two general methods have been employed for making bifunctional chelates form chelating agents. In the first method one or more carboxylic acid groups of a polyaminopolycarboxylic acid chelator are activated by conversion to such activating groups as internal or mixed anhydrides, activated esters (e.g., p-nitrophenyl, N-hydroxysuccinimide, etc.) or with other derivatives known to those skilled in the art. The activated acid group is then added to the protein-chelator complex.

On page 11, please replace ~~the first~~ chemical formula with the following:



Please replace the paragraph beginning on page 16, line 14 to page 17, line 5 with the following paragraph:

The methods of linking the bifunctional chelate to the antibody or antibody fragment are known in the art (Brechbiel, same reference as referred to hereinabove) and will depend primarily on the particular bifunctional chelate and secondarily on the antibody or fragment thereof. For example when the formula Ia compound is R_1 = H, R_2 = -NCS or -NHC(=S)NHR$_{12}$, one reacts 10 μL of a 5.0 mM aqueous solution of the formula I chelator with 0.5 mL of a 5.0 mg/mL monoclonal antibody (B72.3 purchaseable from Damon Biotech Corporation) in 50 mM Hepes buffer at ph 8.5. 16 μL of 1.5M aqueous triethylamine is added. After 2 hours reaction time, the monoclonal antibody is purified by dialysis. This procedure provides between 1 and 2 formula I chelator molecules bound to each monoclonal antibody.

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Radioactive metal ion (for example ^{90}Y) can then be added to the monoclonal antibody-bound chelator by methods known in the art. For example, ^{90}Y as the $^{90}Y(III)$ $(acetate)_3(H_2O)_4$ approximate formula in aqueous solution) can be reacted with the monoclonal antibody-bound chelate in solutions where the concentration of each is between 10^{-5} and $10^{-7}M$ and the pH is 6. Dialysis against citrate is then used to purify the product.

A4 cd

Please replace the paragraph beginning on page ~~17, line~~ 6 to line 27 ~~with~~ with the following paragraph:

An alternative, and preferred method follows that described above, but substitutes the metal-chelate complex for the chelating ligand. To use this metal the metal chelate complex is first made by reacting metal-oxide, -halide, -nitrate, -acetate, or the like with formula I chelator. For the chelator described above the acetate of ^{90}Y at $<10^{-6}M$ is reacted with the chelator at about $10^{-3}M$ at pH 6, the chelate complex is purified by ion exchange or reverse phase HPLC chromatography, and then reacted and then reacted with the monoclonal antibody described above for the chelator. The bifunctional, metal-containing, linked antibody is used in the following manner. A human or animal with a tumor to which the monoclonal antibody is specific is injected intravenously, subcutaneously, intraperitoneally or intralymphatically for example, with an aqueous solution of the ^{90}Y-formula I chelator-monoclonal antibody compound. This allows the radioactive metal ion to be directed to the tumor for which it is intended. The intravenous dosage used is 0.1 to 0.4 millicuries per kilogram of body weight.

A5

On page 31, please replace ~~lines~~ 30-31 with the following:

A. N,N'-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]-ethyl]-5-nitro-1, 3-benzenedicarboxamide

A6

On page 41, please replace lines ~~2-6~~ with the following:

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A7 Data on Water Soluble Gd Complexes and Ions Demonstrating the Enhancement of Relaxivity by N-Hydroxyalkyl or N-alkyl-isophthalamide Groups and by Aryl Groups or by Hydroxyalkyl or Alkylamido Groups.

On page 42, please replace ~~lines~~ lines 7-8 with the following:

A8 A. N,N'-Bis(2-methylbutyl)-5-[[(phenylmethoxy)-carbonyl]-amino]-1,3-benzenedicarboxamide

On page 42, please replace lines ~~26-28~~ with the following:

A9 B. N,N'-Bis(2-methylbutyl)-5-[methyl [(phenyl-methoxy)carbonyl]amino]-1,3-benzende-carboxamide

On page ~~49~~, please replace lines 16-~~18~~ with the following:

A10 B. 10-[N-(4-Nitrophenyl) acetamido]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt

On page ~~57~~, please replace lines 16-19 with the following:

A11 10-[2-[[3,5-Bis[[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid-gadolinium (III) complex

On page 57, please replace lines 21-22 with the following:

A12 A. N,N'-Bis(2-hydroxyethyl)-5-nitro-1,3-benzenedicarboxamide

On page 58, please replace lines 1-2 with the following:

A13 B. N,N'-Bis(2-acetoxyethyl)-5-amino-1,3-benzenedicarboxamide

On page ~~59~~, please replace lines 11-12 with the following:

A14 D. 5-[(Chloroacetyl)amino]-N,N'-bis(2-hydroxy-ethyl)-1,3-benzenedicarboxomide

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Please replace the paragraph beginning on page 59, line 13 to line 21 with the following paragraph:

A solution of N,N'-bis[2-(acetyloxy)ethyl]-5-[(chloroacetyl)amino-1,3-benzenedicarboxamide (6.2 g, 14 mmol) in MeOH (20 mL) was treated with NaOMe (600 mg, 10.5 mmol). After 2 hours at room temperature, the mixture was neutralized with AG-50W-X2 (H^+ form) resin. The resin was removed by filtration and the solution was evaporated to dryness to afford 4.8 g of crude material. An analytical sample of the title D product was crystallized from MeOH.

A15

On page 59, please replace lines 29-32 with the following:

A16

E. 10-[2-[[3,5-Bis[[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, monosodium salt.

On page 60, please replace lines 22-25 with the following:

A17

F. 10-[2-[[3,5-Bis[[(2-hydroxyethyl)amino]-carbonyl]phenyl]amino]-2-oxoethyll]-1,4,7,10-monogadolinium salt (VII).

IN THE CLAIMS

Please cancel claims 5, 7-10, 13-38 and 40-50 without prejudice or disclaimer and amend the following claims:

A18

1. (amended) A diagnostic agent comprising an aminocarboxylate ligand complexed with a paramagnetic metal ion wherein a nitrogen atom within said aminocarboxylate is substituted with a group comprising an aromatic amide containing at least one substitution on the aromatic ring, the substitution comprising a group of 3 or more non-hydrogen atoms.

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